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AI- enabled *in-vitro* characterization: Shaping the future of solid dosage form

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Abstract
A solid dosage form is a therapeutic formulation in which the active pharmaceutical ingredient and excipients are delivered in a stable solid state (e.g. tablets, capsules, powders, granules). These forms are widely used because they are relatively easy to manufacture, transport, handle, store, and administer and they tend to improve patient compliance due to convenience and precise dosing. *In vitro* characterization of solid dosage form refers to laboratory-based testing of pharmaceutical products like tablets and capsules to assess their physical, chemical and biopharmaceutical properties. These tests are critical for ensuring product quality, stability and performance prior to *in vivo* studies. However, conventional *in vitro* methods often face limitations including lack of accuracy, limited precision, poor reproducibility of *in -vivo* behaviour which can hinder efficient formulation development and quality control. Artificial Intelligence [AI] offers transformative potential by optimizing and predicting *in vitro* performance of solid dosage forms. AI models can quickly analyse large formulation and test datasets, find patterns and predict outcomes like dissolution profiles or bioavailability with high accuracy. Various AI tools and techniques include Machine Learning, Deep Learning, Cheminformatics and QSAR modelling. This review article elaborates on the fundamentals of *in vitro* characterization of solid dosage forms, highlights its limitations, explores the integration of Artificial Intelligence in addressing these challenges and discusses the tools and technologies that are shaping the future of pharmaceutical formulation and testing.

Keywords: AI tools, PBPK/PKPD/QSP modelling, regulatory guidance, design of experiments, organoid AI, *In vitro* dissolution profile

1. Introduction
Artificial Intelligence (AI) is a promising strategy for enhancing pharmaceutical product development and has proven to be a versatile tool with algorithms applicable to solid dosage forms such as tablets, capsules and powders. It plays a significant role in drug discovery, formulation design, manufacturing, quality control, clinical trial management and drug delivery [1]. By definition, AI is a computational process that simulates human intelligence through machines, a concept first introduced in 1956 at a conference led by Marvin Minsky and John McCarthy. A typical AI workflow involves four essential steps: data collection and preparation, AI modelling, simulation and testing and final deployment. Deep Learning (DL), a more advanced subfield of ML (Machine Learning), is based on layered algorithms known as Artificial Neural Networks (ANNs) [2]. These networks, inspired by the biological neuron structure of the human brain, demonstrate superior computational power and predictive accuracy compared with conventional ML models. Solid dosage forms typically consist of one or more APIs combined with suitable excipients, including binders, disintegrants, stabilizers, antioxidants and granulating agents. The development of solid dosage forms is a highly complex process that requires an in-depth understanding of physicochemical characteristics and pharmacokinetic/pharmacodynamic (PK/PD) profiles. It generally involves several stages, such as preformulation studies, product development and large-scale manufacturing [3, 4].

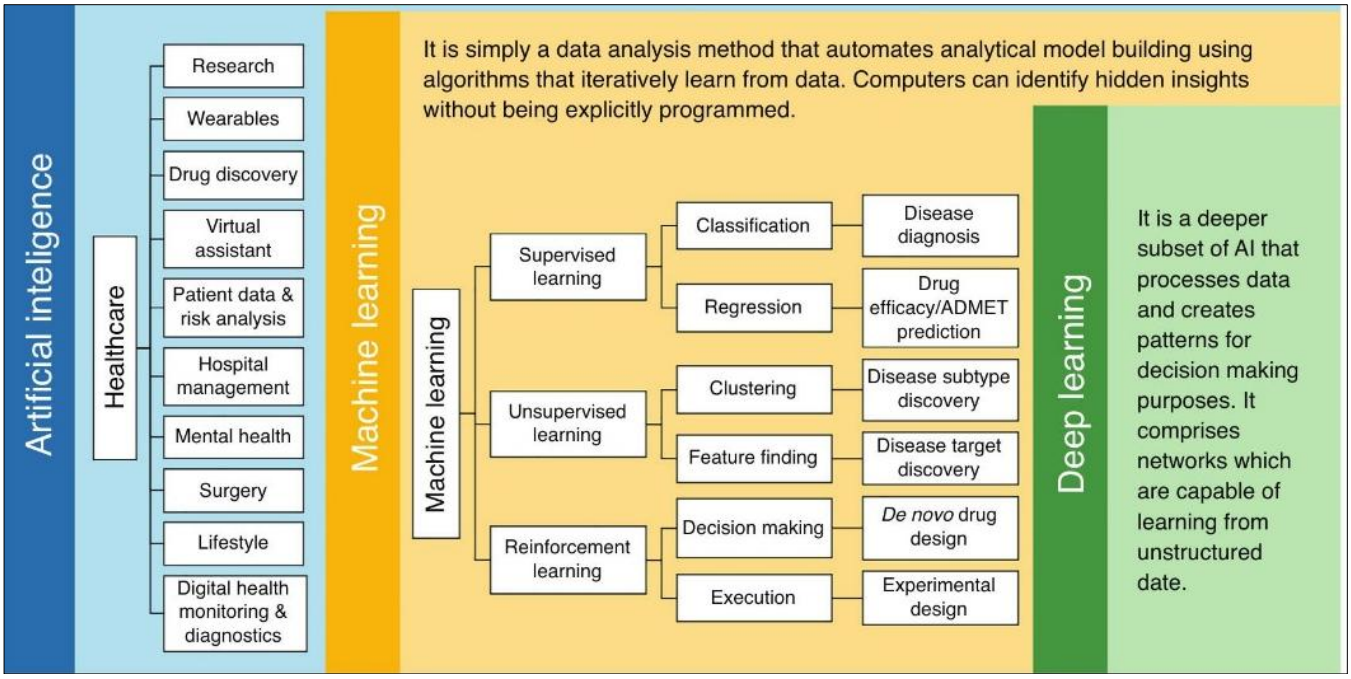


Fig 1: Artificial Intelligence in drug development

2. Challenges in conventional *in-vitro* methods of solid dosage forms

A drug's effectiveness in oral therapy relies primarily on its solubility and permeability, which govern absorption, bioavailability and therapeutic outcome. For solid dosage forms, dissolution in gastrointestinal fluids is the critical first step toward absorption. Insufficient solubility often leads to poor or variable bioavailability [5]. Drugs that are highly hydrophilic or structurally bulky face challenges in crossing the intestinal epithelium. It is estimated that about 40% of marketed drugs and nearly 90% of pipeline candidates exhibit poor aqueous solubility. These limitations create significant hurdles in developing efficient oral solid dosage forms. The traditional trial-and-error strategy for formulation development is therefore slow, resource-intensive, and inefficient. Developing PDDS and accurately predicting their release profiles is challenging because of their complex structures and multiple influencing factors, while conventional mathematical and empirical methods fall short in addressing these complexities [6]. *In vivo* bioequivalence (BE) studies are essential to establish equivalence between generic and innovator products, but for highly variable drugs, direct testing in subjects often carries a high risk of failure [7].

3. AI tools for *in vitro* characterization

Growing collaborations between artificial intelligence (AI)-driven and machine learning (ML)-focused organizations and pharmaceutical companies are significantly streamlining and advancing the drug development process (Jiang). In this study, the following software tools were employed: DD Solver (Dissolution Data Analysis Software Solver, an Excel add-in for both model-dependent and model-independent dissolution analysis), Design-Expert (for experimental design and optimization), Gastro Plus (for physiologically based pharmacokinetic and pharmacokinetic simulations), and MATLAB (Matrix Laboratory, a high-level computing environment for data analysis, modelling, and simulation) [8].

Dissolution profile comparison was performed using the similarity factor (f_2), expected similarity factor ($\hat{f}_2$, exp), and bias-corrected similarity factor ($\hat{f}_2$,bc). The f_2 factor quantifies the similarity between test and reference profiles, with values of 50–100 indicating equivalence. The $\hat{f}_2$, exp provides an adjusted estimate accounting for variability across multiple dissolution tests, while $\hat{f}_2$, bc incorporates bootstrapping methods to correct for bias in highly variable data. These parameters were calculated using DD Solver, Bootf2BCA (Bootstrap f_2 Bias-Corrected and Accelerated, a resampling-based method for reliable f_2 estimation), and PhEq_bootstrap (Pharmacokinetic/Pharmaceutical Equivalence Bootstrap, a tool for assessing equivalence of dissolution profiles with variability considerations). DD Solver was further applied for model-dependent kinetic analyses [9].

Fig 2: Drug product development in collaboration with AI and pharmaceutical companies

3.1 DD Solver

DD Solver is a free Excel add-in (VBA-Visual Basic for Applications) designed specifically to model and compare in-vitro drug dissolution and release profiles. It includes approximately 40 common empirical and semi-empirical models, along with several model-independent comparison methods, allowing users to fit, compare, and report dissolution data without custom coding [10].

a) **Utilities of the software**

- Performs non-linear regression to fit percentage of drug released versus time to various models (zero- and first-order, Higuchi, Hixson-Crowell, Weibull, Korsmeyer–Peppas, etc.).
- Computes goodness-of-fit (GOF) metrics (R^2, adjusted R^2, AIC, MSC), residual plots, and confidence intervals (CIs) for parameters.
- Implements model-independent comparisons (f_1, f_2, Rescigno indices, multivariate distance) and bootstrap f_2 approaches for highly variable data.
- Facilitates testing mechanistic hypotheses (e.g., diffusion vs. erosion) and quantification of model fit [9].

b) **Software inputs and outputs**

- **Input:** Dissolution dataset (time points × replicate percentage of drug released), optional weights/limits.
- **Output:** Best-fit parameter estimates, fitted curves, residual diagnostics, model ranking tables, and similarity metrics ready for reporting or publication [8].

c) **Applications in pharmaceutical sciences**

- Mechanistic screening of candidate formulations (identify the model that best describes release and interpret parameters).
- Compare batches or strengths, determine initial *in vitro–in vivo* correlation (IVIVC) candidates via empirical fits.
- Support publications and regulatory submissions with fitted parameters and statistical analyses.
- Widely used in academia and by generic R&D groups for dissolution modelling and f_2/bootstrap comparisons; cited in AAPS and DD Solver literature as a standard tool for dissolution profile comparison [9].

3.2 Design-Expert (Stat-Ease)

Design-Expert is a commercial design of experiments (DOE) software package for planning, analysing, and optimizing multifactor experiments, including screening designs, factorials, response surface methodology (RSM), mixture designs, and combined designs. It integrates ANOVA (Analysis of Variance), regression diagnostics, contour/response-surface plotting, and desirability optimization into a streamlined workflow [12].

Utilities of the software

- Constructs optimal experimental matrices (2-level factorial, fractional factorial, Box-Behnken, central composite design [CCD], mixture designs).
- Fits polynomial response models and performs ANOVA to identify significant main effects and interactions.
- Generates contour and 3D response-surface plots.
- Computes multi-response desirability to determine factor settings that meet several specifications simultaneously [13, 15].

Software inputs and outputs

- **Input:** Selected factors with defined ranges (formulation/process variables) and measured responses.
- **Output:** ANOVA tables, regression equations, diagnostic plots, contour/response-surface visualizations, optimum factor settings, and predicted responses (with confidence intervals) [18].

Applications in pharmaceutical sciences

- Screening excipients and process variables (binder percentage, polymer level, compression force).
- Optimizing granulation and tableting parameters for hardness, dissolution, and disintegration.
- Defining QbD design space and reducing experimental runs compared with traditional OFAT (one-factor-at-a-time) methods.
- Widely used across pharmaceutical formulation and process R&D; published studies and vendor case studies demonstrate optimization of wet granulation, tablet coating, and continuous manufacturing variables. Stat-Ease provides multiple case studies illustrating industrial applications [19].

3.3 Gastroplus (Simulations-Plus)

Gastro Plus is a commercial physiologically based biopharmaceutics/pharmacokinetics (PBPK/PBBM) simulation platform that mechanistically links in-vitro dissolution, drug physicochemical properties (solubility, dissociation constant pKa, permeability), formulation attributes, and gastrointestinal (GI) physiology to predict in-vivo absorption and systemic pharmacokinetics (maximum plasma concentration *Cmax*, time to reach maximum plasma concentration Tmax, area under the plasma concentration–time curve *AUC*) across virtual populations and dosing conditions [11].

Utilities of the software

- Contains mechanistic GI modules, including ACAT (Advanced Compartmental Absorption and Transit) and compartmental transit models.
- Includes solubilization and precipitation modules, permeability/absorption models, first-pass metabolism, and full PBPK capabilities.
- Supports *in vitro–in vivo* correlation (IVIVC) building and deconvolution, sensitivity analysis, virtual bioequivalence (BE) simulations, and fed/fasted state modelling.
- Users input in-vitro dissolution profiles, drug properties, and formulation parameters, then calibrate and verify models using any available in-vivo data.

Software inputs and outputs

- **Inputs:** Dissolution data, solubility versus pH, pKa, partition coefficient (logP), particle size, dose/formulation details, and physiological settings.
- **Outputs:** Predicted plasma concentration–time profiles, fraction absorbed, sensitivity plots, IVIVC/deconvolution results, and virtual BE statistics for different populations or food states [14].

Applications in pharmaceutical sciences

- Selection of formulation strategies (immediate-release vs. modified-release formulations).
- Prediction of the impact of particle size, coating, or solubility changes on systemic exposure.
- Risk assessment (e.g., impact of slower dissolution on drug absorption).
- Construction and verification of IVIVC for extended-release (ER) products.
- Simulation of fed versus fasted state effects on absorption [11, 15].
- Support for regulatory dossiers and justification for reduced in-vivo testing.

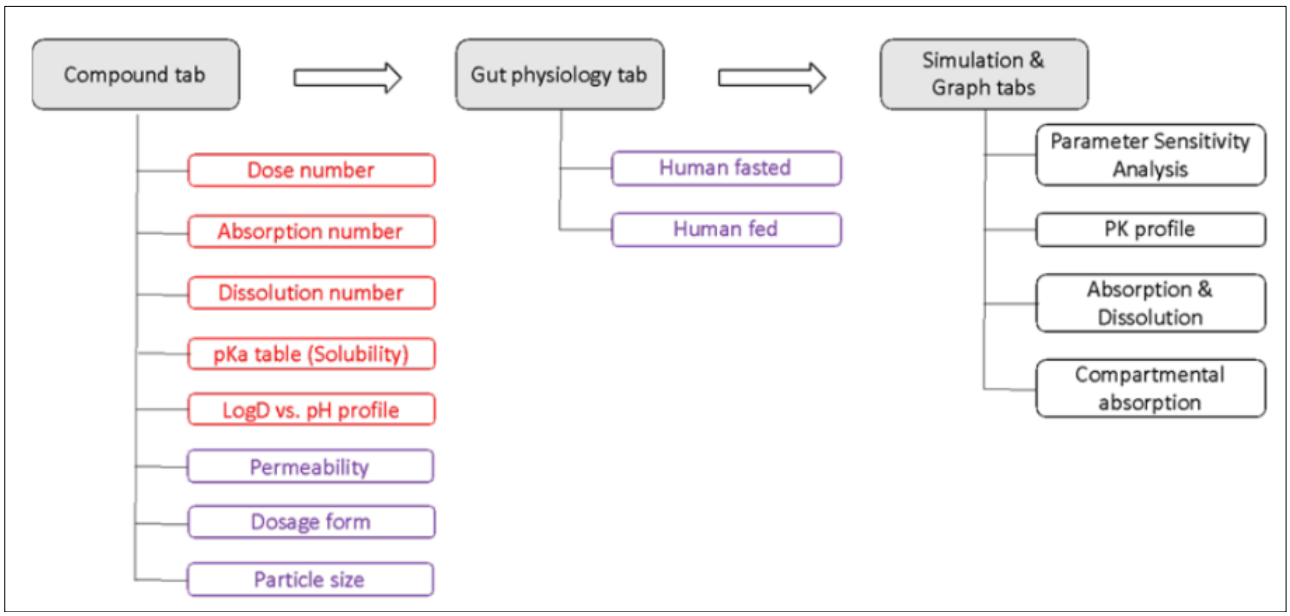


Fig 3: Gastroplus Simulation Workflow

3.4 Matlab (Mathworks) — with Simbiology / Toolboxes

It is a high-level numerical computing platform and language; with Sim Biology and other toolboxes it becomes a flexible environment for building mechanistic PK/PD, PBPK, systems pharmacology and release/distribution models using ODE/PDE (Ordinary/Partial Differential Equation Solvers) solvers, statistical toolboxes and optimization algorithms [16].

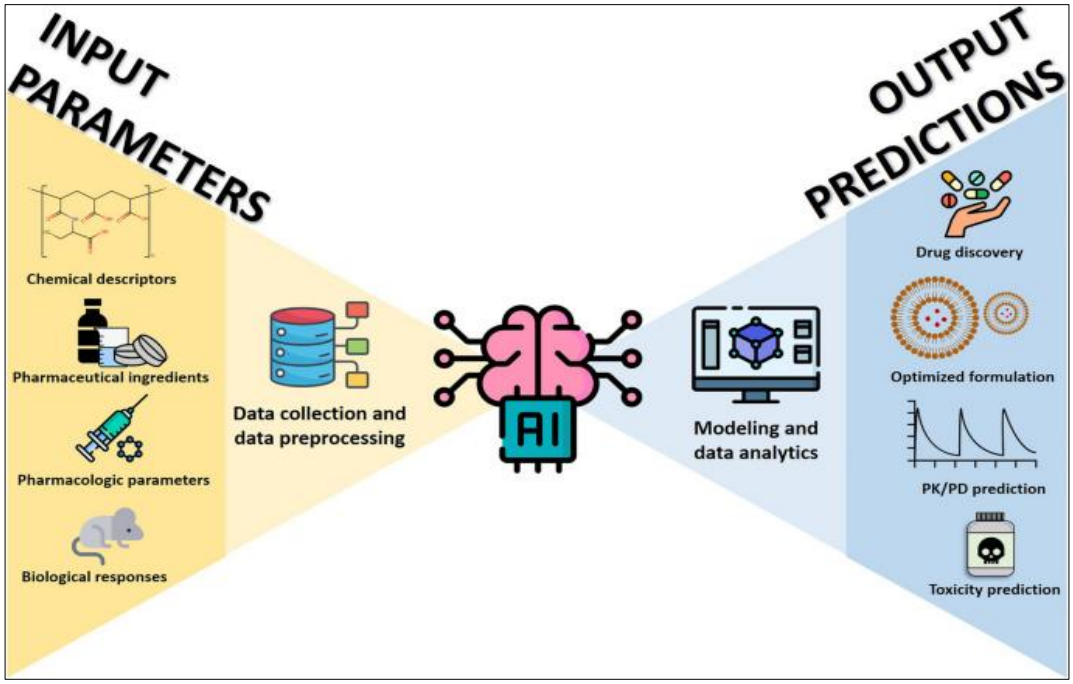
Utilities of software

Numerical solvers (ODE15s, PDE tools), optimization (lsqcurvefit, fmincon), statistics & machine learning, Monte-Carlo/bootstrapping, and SimBiology's graphical model builder for PK/PD and compartmental model.

Fig 4: Detection of Tablet chipping using Neural networks

Users can code custom mechanistic release models (diffusion, swelling, erosion), couple them to PBPK compartments, and run parameter estimation or population simulations. Detect Image Anomalies Using Explainable One- Class Classification Neural Network" and involves training an anomaly detector for visual inspection of tablet images [17,22].

Software inputs and outputs



Inputs: experimental data, model structure (equations or block diagram), initial parameter guesses; Outputs: fitted parameter values, simulated concentration/time profiles, sensitivity and uncertainty analyses, figures and exportable numerical results [20,21].

Fig 5: Mapping Inputs to Outputs in Pharmaceutical Research and Drug development using AI

Applications in Pharmaceutical sciences

Mechanistic modelling of matrix swelling/diffusion, linking in-vitro dissolution to plasma PK via bespoke PBPK code or Sim Biology models, Monte Carlo variability studies for formulation robustness, and advanced statistics or ML models for PAT (Process Analytical Technology) / QbD (Quality by Design) pipelines. Large pharma (e.g., Pfizer) use MATLAB + Sim Biology for model-based drug development and PK/PD workflows [23].

MATLAB/Sim Biology is used in both industry and academia for PBPK/PKPD/QSP (Physiologically Based Pharmacokinetics / Pharmacokinetics/Pharmacodynamics / Quantitative Systems Pharmacology) modelling; Pfizer and others publish user stories on model-based decisions aided by MATLAB workflows [36].

3.5 Pheq_Bootstrap / Bootf2bca (Bootstrap F_2 Tools)

PhEq_bootstrap and Bootf2bca are software tools that implement bootstrap (and bias-corrected accelerated — BCa) methods to estimate the distribution and confidence intervals of the dissolution similarity factor f_2, addressing the limitations of the standard f_2 when dissolution data are highly variable. They allow reporting of 90% CIs (or other percentile intervals) for f_2 rather than a single point estimate [24].

Utilities of software

For a given test and reference dissolution dataset (usually n ≥ 12 units), the tools resample (with replacement) many bootstrap datasets, compute f_2 for each replicate, then derive bootstrap mean/median and percentile or BCa confidence intervals; some implementations also calculate variance-stabilized metrics or model-dependent comparisons (MSD) to handle edge cases. This gives an uncertainty quantification for similarity claims [25].

Software inputs and outputs

Inputs: raw unit-level dissolution data (timepoints and per-unit percentage of drug dissolved), bootstrap settings (N resamples), truncation rules; outputs: bootstrap f_2 distribution, point estimate(s), Lower and Upper Confidence Interval (CI) Bounds and decision criteria (e.g., lower 90% CI ≥ 50 → similarity) [33].

Applications in Pharmaceutical sciences

During generic formulation comparisons, batch comparability studies and regulatory submissions when standard f_2 is unreliable due to high variability; supports justifying biowaiver decisions or guiding formulation endpoints by quantifying uncertainty. Regulatory guidance (Food and Drug Administration/European Medicines Agency) still references $f_2 = 50$ as similarity threshold but explicitly recognizes limitations and alternative approaches when variability is high [34].

Comparative studies and peer-review papers evaluating bootstrapped f_2 methods recommend PhEq_bootstrap/Bootf2bca when variability is large; reviewers of generic product dossiers increasingly expect robust statistical treatment of f_2 where variability is an issue [26, 32].

3.6 Drug Flow (AI-Driven Platform)

Drug Flow is a cloud-based, AI-powered one-stop platform designed to accelerate early-stage drug discovery by integrating advanced machine learning algorithms with traditional physics-based methods, making computational tools accessible to non-experts in pharmaceutical research.

Utilities of software

Drug Flow streamlines workflows through modules for molecular docking, Quantitative Structure Activity Relationship modelling, de novo molecular generation, ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) prediction, and virtual screening, enabling automated hit identification, lead optimization, and comprehensive property assessment to reduce manual experimentation and enhance innovation in drug design.

Software inputs and outputs

Experimental inputs include protein structures, provided as Protein Data Bank (PDB) files or uploaded models, as well as ligands, represented as Simplified Molecular Input Line Entry System (SMILES) strings, MOL files, or manually drawn chemical structures. Additional inputs comprise chemical libraries, such as those from Enamine or Chem Div, training datasets for quantitative structure–activity relationship (QSAR) modelling, including molecular fingerprints like extended-connectivity fingerprints of diameter 4 (ECFP4) and molecular descriptors calculated using RD Kit, reference fragments for molecule generation, and definitions of binding sites on target proteins. The computational pipeline outputs docking scores and poses, visualized using tools such as Mol*, absorption, distribution, metabolism, excretion, and toxicity (ADMET) predictions across 76 parameters presented in color-coded tables, QSAR model metrics such as receiver operating characteristic area under the curve (ROC-AUC) and coefficient of determination (R^2) along with predictions, generated or filtered molecules ranked according to scaffold structures, and results from virtual screening, including clustered compounds and summarized molecular properties [44].

Applications in pharmaceutical sciences

Supports hit-to-lead optimization, toxicity forecasting, and high-throughput virtual screening for novel therapeutics, particularly in oncology and infectious diseases; used to predict binding affinities, assess drug-likeness, and design patient-specific candidates, minimizing failure rates in preclinical pipelines.

3.7 Organoid AI Models (AI-Enabled Organoids)

Organoid AI models, or AI-Enabled Organoids, represent an integrated framework combining 3D organoid cultures with artificial intelligence (particularly machine learning and deep learning) to mimic organ architecture and functions for advanced biomedical modelling, overcoming limitations in traditional 2D cultures and manual analyses.

Utilities of software

Facilitates rapid optimization of organoid construction via AI-driven screening of matrices, growth factors, and stimuli; automates multiscale image feature extraction for morphology assessment; streamlines multi-omics integration (genomics, proteomics) for data analysis; and enables predictive modelling for drug responses and disease progression, enhancing scalability and precision in tissue engineering [45].

Software inputs and outputs

Experimental datasets include imaging data, such as bright-field microscopy and immunofluorescence (IF) imaging, as well as multi-omics profiles, including single-cell RNA sequencing (scRNA-seq) for transcriptomic analysis and metabolomics for metabolic profiling. These datasets also incorporate culture conditions, including variations in growth factors such as Wingless-related integration site proteins (WNTs) and Bone morphogenetic proteins (BMPs), as well as environmental parameters like temperature. External stimuli, such as mechanical and electrical stimulation, are also considered. Historical experimental data are used to train machine learning (ML) models, including convolutional neural networks (CNNs) and generative adversarial networks (GANs). The pipeline generates outputs including optimized experimental protocols, such as recommended matrix compositions and cell type ratios, quantified features such as porosity, cell counts, and spatial heterogeneity, integrated omics insights including gene correlations and biomarkers, and predictive metrics such as neurotoxicity scores and drug efficacy rankings, accompanied by confidence intervals (CI) to indicate the statistical reliability of predictions.

Applications in pharmaceutical sciences

Revolutionizes drug screening and toxicity testing using patient-derived organoids for cancers (e.g., colorectal) and neurodegenerative diseases; supports personalized medicine by modelling disease mechanisms, identifying targets, and evaluating therapeutics in human-relevant systems, reducing animal testing and accelerating clinical translation [26].

Table 1: AI Tools used in *in-vitro* studies of Solid dosage forms

Software	Founder / Company & Year	Application	Product
DD Solver	Computational pharmaceutics researchers, Excel add-in (VBA), ~2010	Modelling & comparing in-vitro drug dissolution profiles; kinetic model fitting; similarity factor (f_2), bootstrapped f_2	Aspirin floating tablets [37] Famotidine gastro-retentive floating tablets [38] Griseofulvin tablets [39] Montelukast tablets [27-30]
Design-Expert	Stat-Ease Inc., 1980s (v11 cited)	Design of Experiments (DoE) for formulation & process optimization	Telmisartan nanosuspensions; Oral solid dosage form optimization [35]
Gastro Plus	Simulations Plus Inc., late 1990s	PBPK / PBBM simulations: IVIVC, virtual bioequivalence, fed/fasted state prediction	Metoprolol extended-release mini-tablets [40] Roche & BMS (Bristol-Myers Squibb) formulation strategies [37,41]
MATLAB (SimBiology)	MathWorks, 1984 (SimBiology toolbox: 2000s)	Mechanistic PK/PD & dissolution modelling; Monte-Carlo simulations; parameter estimation	Pfizer model-based drug development integrating dissolution & PBPK [31]
PhEq_bootstrap / Bootf2bca	Academic development, 2000s	Bootstrap f_2 analysis; confidence interval for dissolution variability; regulatory biowaiver support	Generic product dissolution comparisons (test vs reference) [42,43]
DrugFlow	Carbon silicon AI Technology Co., Ltd., ~2022	AI-driven platform for early-stage drug discovery; integrates molecular docking, QSAR modelling, de novo generation, ADMET prediction, and virtual screening	Hit-to-lead optimization in oncology (e.g., kinase inhibitors); toxicity forecasting for infectious diseases (e.g., COVID-19 repurposed drugs) [44]
Organoid AI Models (AI-Enabled Organoids)	Long Bai *et al*. (Shanghai University)2024	AI integration for organoid construction, multiscale image analysis, multi-omics data processing, and preclinical evaluation; optimizes matrix gels, cell culture, and disease modelling	Brain organoids for neurotoxicity prediction (e.g., Parkinson's disease models); kidney organoids for ciliopathic renal phenotype validation; colorectal cancer organoids for drug efficacy testing [45]

4. Future Outlooks

The future of in-vitro characterization is shifting from physical lab work to a predictive digital ecosystem, where AI will become the backbone of formulation science [46]. This transformation will be driven by the creation of "digital twins" for dosage forms, allowing for virtual simulation and optimization before any physical product is made. Integrated with Process Analytical Technology (PAT), AI will enable real-time quality control during manufacturing, while advanced models like Organoid AI will offer more human-relevant preclinical data, reducing animal testing [47]. Ultimately, this convergence of data-driven intelligence and pharmaceutical innovation will accelerate the development of personalized therapies through technologies like 3D-printed medicines, revolutionizing how solid dosage forms are designed, tested, and delivered to patients [48].

5. Conclusion

Artificial Intelligence (AI) has emerged as a transformative force in pharmaceutical sciences, particularly in the *in vitro* evaluation of solid dosage forms ranging from granules, conventional and orally disintegrating tablets, solid dispersions, and capsules to advanced 3D-printed drug delivery systems. By leveraging models such as Artificial Neural Networks (ANNs), Convolutional Neural Networks (CNNs), Support Vector Machines (SVMs), and Deep Neural Networks (DNNs), AI has demonstrated remarkable accuracy in predicting dissolution profiles, detecting structural defects, ensuring content uniformity, forecasting stability, and enabling real-time monitoring through spectroscopic tools like Near-Infrared (NIR) and Raman spectroscopy. Future directions point toward the integration of AI with Process Analytical Technology (PAT), the creation of digital twins for dosage forms, and the personalization of therapies through 3D-printed medicines, signalling a shift where predictive modelling may replace much of conventional *in vitro* testing. While regulatory acceptance is still evolving, AI is rapidly moving from a supportive role to becoming the backbone of formulation science, driving real-time quality control, accelerating optimization, and enabling patient-specific therapies. Ultimately, by bridging data-driven intelligence with pharmaceutical innovation, AI is set to revolutionize the development, testing, and optimization of solid dosage forms, shaping the future landscape of drug delivery and therapeutic performance.

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